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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,184	03/05/2002	John H. Lawrence III	47746-C	1657

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BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,184	LAWRENCE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,27,37-39,47,52,55 and 61-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *47,52,55,92-99 and 112-117* is/are allowed.

6)☒ Claim(s) *1, 5, 27, 37-39, 47, 61-91, 100-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The specification, claims 1, 5, 27, 37, 47, 52, 61, 62, 65-68, 71 have been amended, claims 76-117 have been added, and claims 48, 53, 54, and 56 have been canceled by the amendment dated 4/29/2004.

Claims 1, 5, 27, 37-39, 47, 52, 55, 61-117 are pending for examination.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5, 27, 61, 66-72, 74, 75 are rejected under 35 U.S.C. 102(a) as being anticipated by Fasano (WO 96/37196).

Fasano teaches a method of employing a capsule containing zonula occludens toxin as a vascular permeability agent and a nucleic acid containing an

attenuated viral DNA for to enhance tissue permeability of the nucleic acid (pages 10, 13, and 16).

To the extent that the claims do recite *per se* an administration of a calcium concentration of any particular concentration of less than 500 micromolar, but rather just recite a characteristic of a tissue intended for the delivery of a nucleic acid, wherein the characteristic describes a concentration of calcium ions is less than 500 micromlar, which includes a zero concentration, the tissue indented for the delivery in Fasano meets the limitation of the claims.

Absent evidence to the contrary, the kits and/or the treatment solution of Fasano and the nucleic acid delivery method of Fasano have all of the properties cited in the claims.

Claims 1, 5, 27, 61, 66-72, 74, 75 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolff (US Pat No. 6,265,387).

Wolff teaches a method of employing a vascular permeability agent such as VEGF to enhance the permeability of a blood vessel within a target tissue *in vivo* thereby increasing the efficiency of the polynucleotide delivery and expression (column 6 through column 7). The patent as a whole teaches numerous kits and/or treatment solutions comprising a vascular permeability agent and a nucleic acid vector.

To the extent that the claims do recite *per se* an administration of a calcium concentration of any particular concentration of less than 500 micromolar, but rather just recite a characteristic of a tissue intended for the delivery of a nucleic acid,

wherein the characteristic describes a concentration of calcium ions is less than 500 micromlar, which includes a zero concentration, the tissue indented for the delivery in Wolff meets the limitation of the claims.

Thus, Wolff anticipates the claims.

Claims 1, 5, 27, 37, 61, 63, 64, 66-73, 75 are rejected under 35 USC 102(e) as being anticipated by Ryan (US 2003/0195495 A1)

Ryan teaches on page 8 a concept of employing a combination of vascular endothelial growth factor, vascular permeability factor, and a gene therapy encoding a VEGF so as to increase permeability, proliferation of vascular endothelial cells, and perfusion and/or delivery of the agents to the cells. Catheter kits comprising these agents are disclosed. In addition, page 8 discloses that donor endothelial cells can be cultured so as to increase the delivery and/or transport and/or permeability of a nucleic acid vector into the cultured cell, and that the cultured and transfected cells can be implanted into a treated subject.

To the extent that the claims do recite *per se* an administration of a calcium concentration of any particular concentration of less than 500 micromolar, but rather just recite a characteristic of a tissue intended for the delivery of a nucleic acid, wherein the characteristic describes a concentration of calcium ions is less than 500 micromlar, which includes a zero concentration, the tissue indented for the delivery in Ryan meets the limitation of the claims.

Thus, Ryan anticipates the claims.

Applicant's response on page 9 has been considered by the examiner but is not found persuasive because the claims are not necessarily limited to an actual step of administering a calcium concentration of less than 500 micromolar but not at zero concentration. A change of an administering step of employing a calcium concentration of between about 40 micromolars and 500 micromolar would obviate the above rejections.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 27, 61-63, 66-87, 102, 105,108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nabel *et al.* (US Pat No. 5,328,47) taken with Wolff, Epstein *et al.* (US Pat No. 6,007,817) or Neufeld *et al.* (US Pat No. 6,013,780).

Nabel *et al.* teach a nucleic acid delivery kit comprising a catheter and a DNA composition comprising a DNA encoding a toxin, and a method of employing the kit for delivering a DNA to a target tumor cells in blood vessels *in vitro* and/or *in vivo* (entire document, column 12, lines 34-37, column 14). More specifically, column 13 discloses that a targeting ligand is complexed to the DNA and that a carrier is coupled to the DNA for enhancing the delivery of the DNA to the target cell. Nabel *et al.* do not teach that a vascular permeability agent is employed in the DNA kit so as to enhance the delivery of the DNA to the target tumor cell.

However, at the time the invention was made, Wolff, Epstein *et al.* or Neufeld *et al.* teach a method of employing a vascular permeability agent (Wolff, columns 6, 7; Epstein *et al.,* IL-2; Neufeld *et al.,* VEGF) for enhancing the delivery of a bioactive molecule to target tumor cells (Epstein *et al.,* columns 3, claim 1; Neufeld *et al.,* column 6). To the extent that the claims do recite *per se* an administration of a calcium concentration of any particular concentration of less than 500 micromolar, but rather just recite a characteristic of a tissue intended for the delivery of a nucleic acid, wherein the characteristic describes a concentration of calcium ions is less than 500 micromlar, which includes a zero concentration, the tissue indented for the delivery in Nabel meets the limitation of the claims.

It would have been obvious for one of ordinary skill in the art to have modified the DNA delivery method Nabel *et al* as a matter of design choice. by employing any

DNA/gene encoding an anti-tumor product and/or known vascular permeability agent, *e.g.,* as exemplified by the prior art disclosed and relied upon by the as-filed application, so as to enhance the delivery of the DNA to target tumor cells. One of ordinary skill in the art would have been motivated to have employed any known vascular permeability agent in the exemplified DNA delivery method Nabel *et al.* because Wolff, Epstein *et al.* or Neufeld *et al.* teaches that vascular permeability agents would enhance the delivery of DNA drugs to the tumor cell.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1, 27, 37, 37-39, 76-91, 110, 111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan taken with Wolff, Epstein *et al.* (US Pat No. 6,007,817) or Neufeld *et al.* (US Pat No. 6,013,780).

Ryan teaches on page 8 a concept of employing a combination of vascular endothelial growth factor, vascular permeability factor, and a gene therapy encoding a VEGF so as to increase permeability, proliferation of vascular endothelial cells, and perfusion and/or delivery of the agents to the cells. Catheter kits comprising these agents are disclosed. In addition, page 8 discloses that donor endothelial cells can be cultured so as to increase the delivery and/or transport and/or permeability of a nucleic acid vector into the cultured cell, and that the cultured and transfected cells can be implanted into a treated subject. Ryan does not teach explicitly that a vascular permeability agent is employed in the culturing conditions would include an

application of a vascular permeability agent so as to enhance the delivery of the DNA into the cultured cells..

However, at the time the invention was made, Wolff, Epstein *et al.* or Neufeld *et al.* teach a method of employing a vascular permeability agent (Wolff, columns 6, 7; Epstein *et al.,* IL-2; Neufeld *et al.,* VEGF) for enhancing the delivery of a bioactive molecule to target cells (Epstein *et al.,* columns 3, claim 1; Neufeld *et al.,* column 6).

To the extent that the claims do recite *per se* an administration of a calcium concentration of any particular concentration of less than 500 micromolar, but rather just recite a characteristic of a tissue intended for the delivery of a nucleic acid, wherein the characteristic describes a concentration of calcium ions is less than 500 micromlar, which includes a zero concentration, the tissue indented for the delivery in Ryan meets the limitation of the claims.

It would have been obvious for one of ordinary skill in the art to have modified the DNA delivery method Ryan *et al* as a matter of design choice. by employing any DNA/gene encoding a protein product such as angiogenic protein, anti-angiogenic protein, ion-channel proteins, and/or known vascular permeability agent, *e.g.,* as exemplified by the prior art disclosed and relied upon by the as-filed application, so as to enhance the delivery of the DNA to target cells. One of ordinary skill in the art would have been motivated to employ a combination of vascular permeability agents and DNA of choice in the exemplified DNA delivery method Ryan. because Wolff, Epstein *et al.* or Neufeld *et al.* teaches that vascular permeability agents would enhance the delivery of DNA drugs to the tumor cell, and because gene transfer

protocols are routinely employed in the prior art for testing expression and therapeutic potential of a DNA of choice *in vitro* and/or *in vivo.*

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's response (pages 3-4) are similar to that of the response applicable to the 102 rejections, and thus, have been discussed *suppra,* and is not found persuasive.

Claims 47, 52, 55, 92-99, and 112-117 are in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER